CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75279

CORRESPONDENCE

ANDA 75-279

Taro Pharmaceuticals USA, Inc.
Attention: Lorraine Sachs, RAC
U.S. Agent for: Taro Pharmaceuticals Inc.
5 Skyline Drive
Hawthorne NY, 10532

21

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Clobetasol Propionate Gel, 0.05%

DATE OF APPLICATION: December 19, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 22, 1997

We will correspond with you further after we have had the opportunity to review the application.

In the interim, please submit a diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Joseph Buccine
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-279
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-330
HFD-92
HFD-615/M.Bennett
HFD-324/M.Lynch

Endorsement: HFD-615/PRickman, Chief, RSB /S/ date 1/20/98
HFD-615, SMiddleton, CSO _____ date 1-13-98
HFD-629, PSchwartz, Sup. Chem. _____ date

ANDA Acknowledgment Letter!

May 26, 1999

TARO PHARMACEUTICALS INC
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland
U.S.A. 20852

ORIG

Attention: Associate Director, FDA, Office of International Programs

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Sir/Madam:

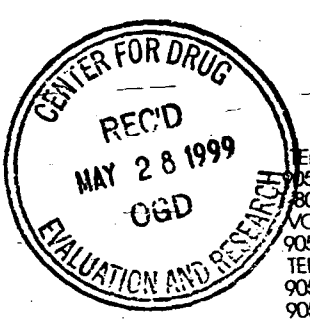
Taro Pharmaceuticals Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced amendment.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned or our U.S. agent,

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Regards,

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs



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May 26, 1999

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Mr. Buccine,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product. Reference is also made to Taro's amendments dated February 15, 1999, February 25, 1999, March 29, 1999, May 3, 1999, May 11, 1999 and May 26, 1999. Reference is also made to a follow-up phone conversation on May 26, 1999, between Dr. Paul Schwartz of the Office of Generic Drugs and Lorraine Sachs of Taro in which it was requested that Taro commit to a maximum thirty (30) day holding period for the bulk product.

Taro at this time, commits to a maximum thirty (30) day holding period for the bulk product. We intend to generate bulk stability data on our first three validation batches with sampling at 1, 2, 3, 6 and 9 month test stations. We plan to file a supplement postapproval for an extension of the holding period.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,
TARO PHARMACEUTICALS INC.

for

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs

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May 11, 1999

Office of Generic Drugs, CDER, FDA
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Rockville, MD 20855-2773

TARO PHARMACEUTICALS IN
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

NDA ORIG AMENDMENT

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Mr. Buccine,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product. Reference is also made to Taro's amendments dated February 15, 1999, February 25, 1999, March 29, 1999 and May 3, 1999. Reference is also made to a phone conversation on May 11, 1999, between Joseph Buccine, Naiqi Ya and Paul Schwartz of the Office of Generic Drugs and Avraham Yacobi, Terry Feldman, Derek Ganes, and Lorraine Sachs of Taro in which the following points were made:

The proposed limit for total impurities of NMT % is not justified, and the limit should be tightened to NMT %, or could be proposed at NMT % with the sum of synthetic precursors included in the calculation.

Taro proposes the limit of NMT % for total degradation products monitored over the shelf-life (22 months) of this product. Synthetic precursors will not be included in the calculation.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

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MAY 12 1999
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Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs

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TARO PHARMACEUTICALS INC.
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May 5, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Mr. Buccine,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product and to Taro's amendments dated February 15, 1999, February 25, 1999, and March 29, 1999. Reference is also made to a phone conversation on April 23, 1999, between you and Lorraine Sachs of Taro in which the following points were made:

Taro's request to extend the expiration dating to 24 months post approval in a CBE supplement based only on the results of the exhibit batch is not acceptable.

Provided in this amendment is recently completed 22 months room temperature stability test data for the exhibit lot S118-5994 in the 15g, 30g and 60g pack sizes (supplementary pages 1-6). After 22 months, total degradation products of about % were seen in each pack size.

Table I: Total Degradation Products for Clobetasol Propionate Gel

Time Point/ Conditions	Total Degradation Products (%)*		
	15 g	30 g	60 g
0 time point			
12 months/ RT			
18 months/ RT			
20 months/RT			
22 months/RT			

***Sum of all impurities excluding synthetic precursors**

Based on the stability data presented in this amendment, Taro requests that a 22 month expiration period be granted for Clobetasol Propionate Gel, 0.05%.

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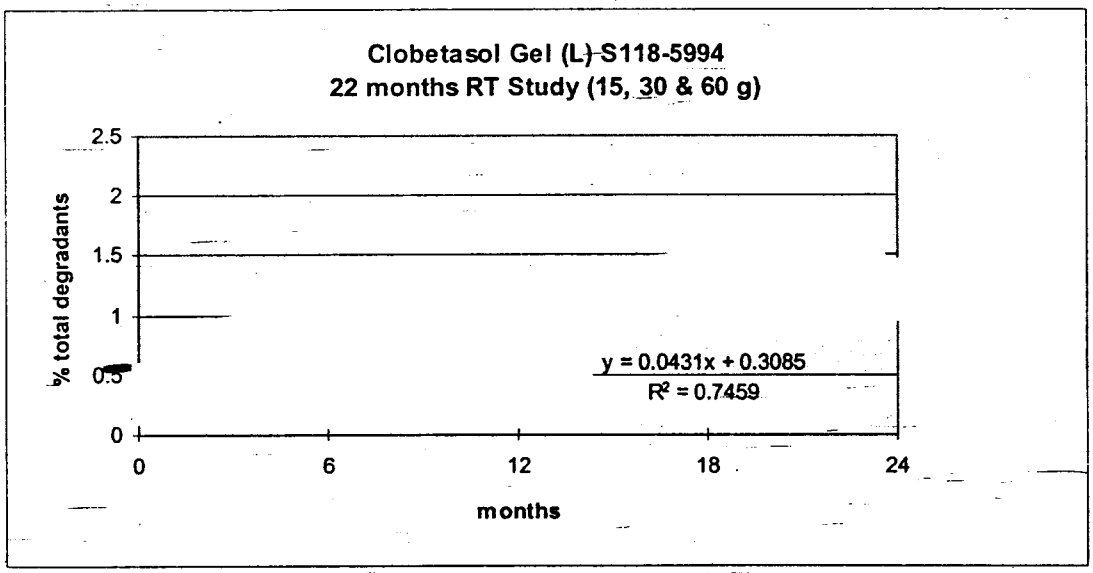
The current limit for total impurities of NMT % is not justified, and the limit should be tightened to NMT %.

Taro has reviewed all stability data to date and now proposes a stability limit of NMT % total degradation products based upon several considerations:

1. The USP monograph for the clobetasol drug substance, attached as supplementary pages 7-8, allows for a limit of not more than % for the sum of all impurities. It is therefore reasonable to expect that after processing the drug substance into a dosage form, the level of degradants may increase. Furthermore, subsequent monitoring of the dosage form over its expected expiry may show further degradation of the active drug substance. Therefore, Taro's proposed stability limit of NMT % for total degradation products in Taro's Clobetasol Gel product is reasonable.

2. Taro's room temperature stability data for % total degradants is represented graphically below including the recently completed 22 month timepoint.



Over the 22 months of study there is a net increase of % total degradants. Should Taro's Clobetasol Propionate Gel be released near the release limit of % (i.e., the 0-time stability station begins with total degradants of %) over 22 months the % total degradants would approach %. We therefore believe that the proposed NMT % limit for total degradants is reasonable.

TARO PHARMACEUTICALS INC.
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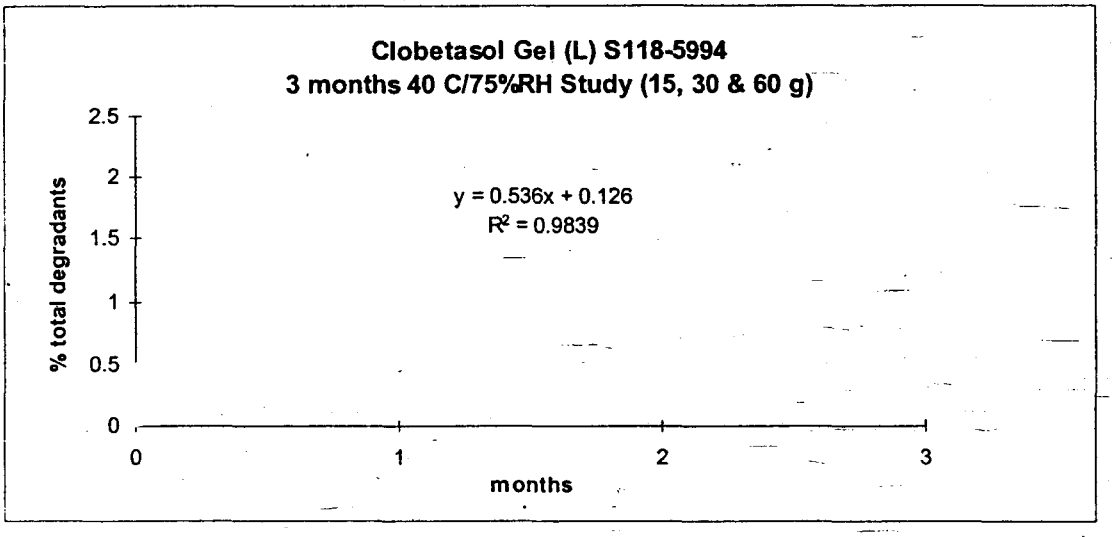
3. Taro understands that any stability specification must be met both over the expiry date of the product (room temperature), and, over any 3 month accelerated stability study used to support post approval change (either within or outside the scope of SUPAC-SS). Taro has previously presented to the Agency the 3 month accelerated stability for exhibit (L) S118-5994 (graphically re-presented below for convenience).



After 3 months, total degradation products amounts approaching % were seen.

Taro proposes that a stability limit of NMT % should be sufficient to accomodate both room temperature and accelerated stability performance, and normal lot-to-lot and analytical method variations.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs

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TARO PHARMACEUTICALS INC.
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March 29, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Mr. Buccine,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product. Reference is also made to Taro's amendments dated February 15, 1999, and February 25, 1999. Reference is also made to a phone conversation on March 3, 1999, between Joseph Buccine, Naiqi Ya, and Paul Schwartz of the Office of Generic Drugs, and Lorraine Sachs and Terry Feldman of Taro. In this conversation the following comments were made by the Office of Generic Drugs (OGD):

The Office of Generic Drugs will only grant an expiration date for this product based on the available room temperature stability data.

Expiration dating to 24 months may be granted post approval provided that supportive room temperature stability data for the exhibit batch is submitted to the OGD.

Please provide data for the innovator product.

Provided in this amendment is recently completed 20 months room temperature stability test data for the exhibit lot S118-5994 in the 15g, 30g and 60g pack sizes (supplementary pages 1-6). After 20 months, total degradation products of about only % were seen in each pack size, which is well within our specification of NMT %.

Table I: Total Impurities for Clobetasol Propionate Gel

Time Point/ Conditions	Total Impurities (%)*		
	15 g	30 g	60 g
0 time point			
12 months/ RT			
18 months/ RT			
20 months/RT			

*Sum of all impurities excluding synthetic precursors

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Three (3) lots of innovator product were analysed (one before its expiration and two after), according to the tests and methods specified on Taro's stability specifications (supplementary pages 7-12). Results from (L) 6J231 (Exp. Sept 98), (L) 6G237 (Exp. Sept 98) and (L) 7K359 (Exp Nov 99) showed total impurities at % and %, respectively.

Based on the stability data presented in this amendment, Taro requests that a 20 month expiration period be granted for Clobetasol Propionate Gel, 0.05%.

Upon completion of the 24 month room temperature test station (due July 99), Taro will submit supportive data to the Agency in a Changes Being Effected Supplement in order to extend the expiration period to 24 months. Thereafter, Taro will continue to monitor the product, as described in our stability protocol, to ensure that it meets all specifications through its expiration date.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs

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March 29, 1999

TARO PHARMACEUTICALS INC
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Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, Maryland
U.S.A. 20852

Attention: Associate Director, FDA, Office of International Programs

Re: **TELEPHONE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Sir/Madam:

Taro Pharmaceuticals Inc. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced amendment.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned or our U.S. agent,

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

Regards,

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

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February 25, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/FA

RE: **ANDA 75-279, Clobetasol Propionate Gel, 0.05%**
Telephone Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application (ANDA) for the above mentioned product, submitted on December 19, 1997, and to a facsimile amendment submitted on February 15, 1999. Reference is also made to a phone conversation on February 15, 1999, between Joseph Buccine, Naiqi Ya, and Paul Schwartz of the Office of Generic Drugs, and Lorraine Sachs of Taro. In this conversation, the following comment was made by the Office of Generic Drugs:

The room temperature stability data that was submitted in the facsimile amendment of February 15 is to the 18 month station. Therefore, the Office of Generic Drugs will only grant an expiration date of 18 months for this product, based upon our previous comment regarding the unacceptability of the accelerated stability data.

Response:

Please note that, as was stated in the phone conference, Taro believes that adequate stability data exists to support a 24 month expiration date for this product. This position is supported by both accelerated and room temperature data as follows:

Accelerated Studies:

In our original ANDA, the results of the 3 month accelerated stability study were presented in tabular form. Figure 1 displays the formation of total degradants over that 3 month period.

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GENERIC DRUGS

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

Figure 1

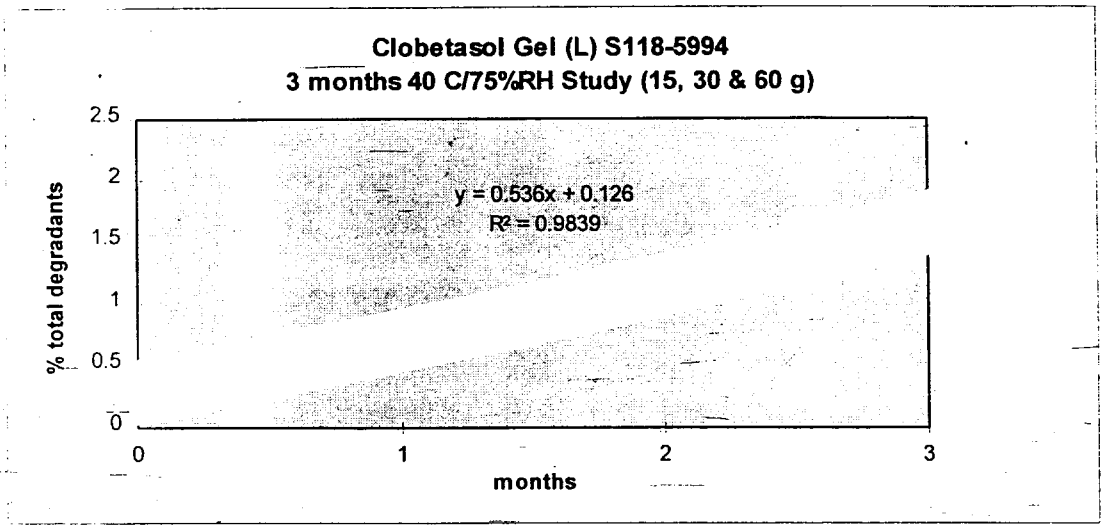


Figure 1 clearly shows that the formation of total degradants is linear, predictable, and, under the stability limit over the 3 month period at 40°C.

In addition, Taro extended the accelerated stability study out to 6 months. This data is displayed in Figure 2.

Figure 2

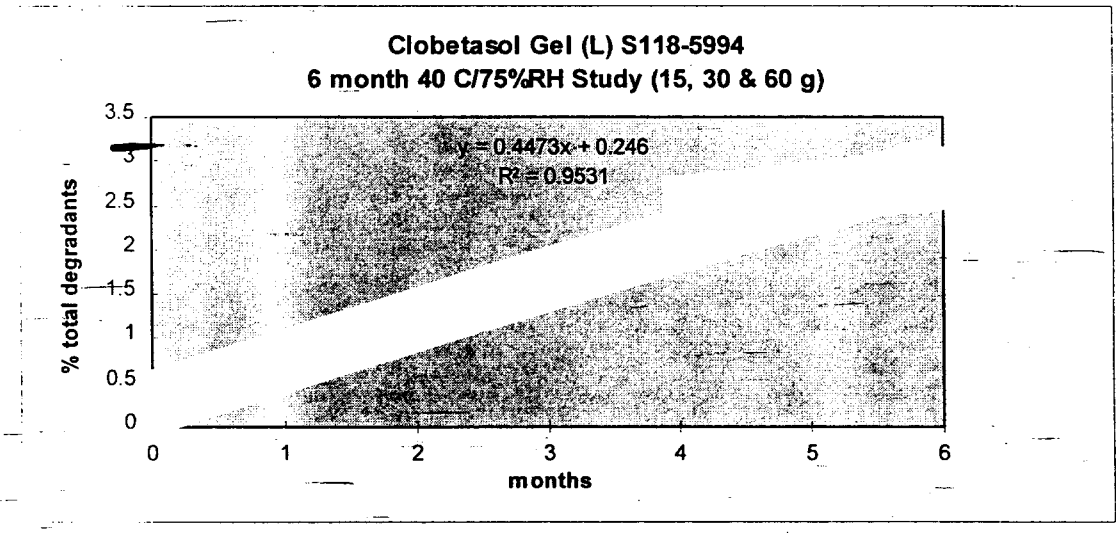


Figure 2 illustrates similar principles as figure 1: the formation of total degradants remains linear and predictable over 6 months at 40°C. Further, this data shows that the stability limit of NMT % total degradants would only be reached or exceeded after approximately 5 months at 40°C.

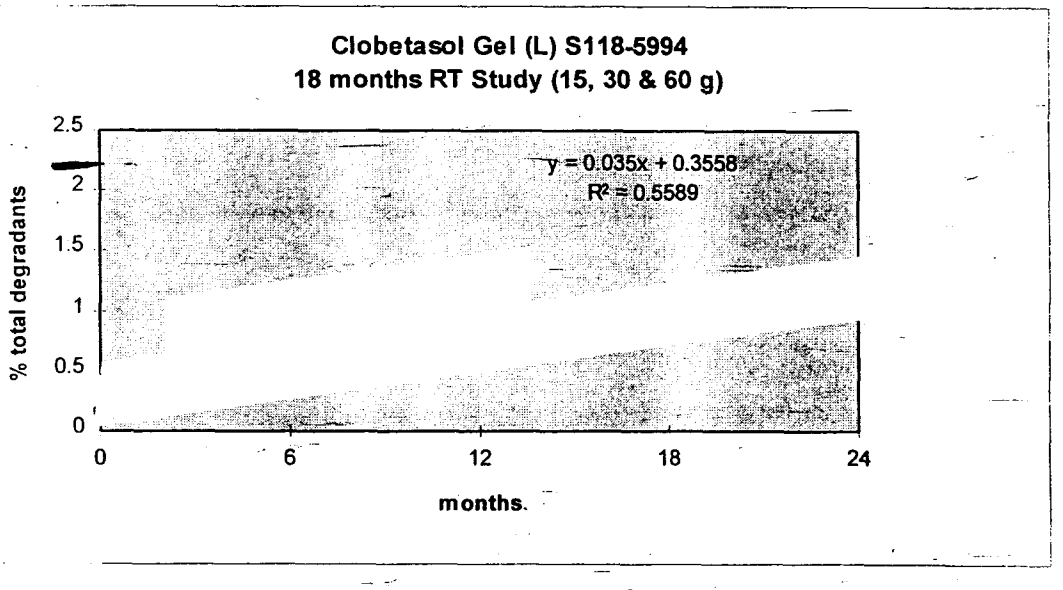
With respect to potency, over the 3 month accelerated period, potency losses of approximately % which were well in the acceptable lower limit of % for the assay were balanced by degradation product increases of about %, thus, mass balance is achieved. Similarly, over the 6 month accelerated study, potency losses of approximately % were balanced by degradation product increases of about %, again supporting mass balance.

Room Temperature:

In our facsimile amendment of February 15, 1999, recently completed (January, 1999) 18 months room temperature stability data for the exhibit lot S118-5994 in 3 pack sizes was presented. After 18 months, total degradation products of about only % were seen in each pack size.

Figure 3 graphically shows the formation of total impurities seen during the 18 month RT study to date for the 3 pack sizes of the exhibit batch. The trend line in figure 3 is also projected out to 24 months and estimates the total degradants level at about %. When the variability of the data is taken into account (through statistical analysis), at 24 months the upper limit of the % confidence level would take the total degradants amount to %.

Figure 3



Additional Supportive Data:

In addition to the data generated for exhibit lot S118-5994, we have data generated for a pilot lot which has the same formulation as the exhibit lot but is a smaller batch size, lot S118-5910. The results for total impurities at the 3 and 6 months accelerated station were, respectively, % , which are comparable to the results obtained for the exhibit lot.

Please also note that, as per our submitted stability protocol, the first three production batches of this product, and annual batches thereafter, will be monitored under our stability program to ensure that the product meets all specifications through its 24 month expiration date. We would not be requesting this dating period unless we had a high level of confidence that the product is capable of maintaining its specifications through 24 months.

We trust that this information is adequate to address your concerns. However, we are available if it is necessary to have a further dialogue regarding this issue.

Sincerely,

Lorraine W. Sachs

Lorraine W. Sachs
Associate Director, Regulatory Affairs

February 25, 1999

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, MD 20852

NEW CORRESP.
NC to FAX

Attention: **Office of International Programs**
Re: **ANDA 75-279**
Clobetasol Propionate Gel, 0.05%
Telephone Amendment

Dear Sir/Madam:

The attached document is being submitted as the field copy for the supplement referenced above. Taro Pharmaceuticals U.S.A., Inc. hereby certifies that this field copy is a true copy of the technical information provided in the supplement. If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

99KS014.DOC
02/25/99 12:41 PM

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

February 15, 1999

TARO PHARMACEUTICALS IN
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Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPD
NC

Re: **FACSIMILE AMENDMENT - ANDA 75-279**
Clobetasol Propionate Gel, 0.05 %

Dear Mr. Buccine,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product. Reference is also made to Taro's amendment submitted August 21, 1998 and to the Agency's correspondence of February 11, 1999, in which FACSIMILE deficiencies were cited.

We now wish to respond to the Agency's comments. For ease of review, the comments are restated in bold and are followed by Taro's response and any necessary supportive documentation.

We trust the information is complete. If you have any further comments, please contact the undersigned or our US agent:

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
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Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ J. Hobbs

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August 21, 1998

TARO PHARMACEUTICALS INC.
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Office of Generic Drugs
Center for Drug Evaluation and Research
Food And Drug Administration
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773
USA

RE: **ANDA 75-279**
Clobetasol Propionate Gel, 0.05%
Major Amendment

Dear Sir,

Reference is made to our Abbreviated New Drug Application (ANDA) for the above referenced product, submitted on December 19, 1997, pursuant to 21 CFR 314.70, and our amendments of February 3, and March 31, 1998. Reference is also made to the Agency's letter of June 2, 1998, in which it is stated that the application is deficient and, therefore, not approvable under Section 505 for the following reasons:

A. Deficiencies:

1. Your viscosity limit for Carbomer 934P, NF is cps which is identical to the viscosity limit for Carbomer 934 NF as described in the current USP/NF. Please clarify.

Response

In preparing the specifications for the excipient Carbomer 934P, NF, incorrect limits for viscosity were indicated by error. We apologize for any inconvenience this may have caused.
Specifications for Carbomer 934P, NF have been revised to include the viscosity limits of 29,400 to 39,400 cps, as per the current NF monograph, and are presented as **supplementary page 1**. Please note that the lot of the Carbomer 934P, used in the exhibit batch of Clobetasol Propionate Gel subject of this ANDA, meets these limits.

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2. Please revise the specifications for Carbomer 934P NF to include the limit of test.

Response

Traditional carbomer resins are polymerized in and therefore, contain residual amounts of The particular grade of carbomer used in this formulation, Carbomer 934P, NF has been manufactured with different solvent systems, toxicologically preferred to Please refer to the Letter from presented in **supplementary pages 2 - 3** and DMF the Letter of Access to which is provided in **supplementary page 4**).

Nonetheless, the manufacturer of the material, has conducted tests to measure residual is an unavoidable contaminant in petroleum based materials and may be present in very low levels in other substances. The levels obtained in these tests were below a limit of ppb *(parts per billion),* whereas the USP limit for is ppm (*parts per million*). assures that the level of will not exceed the USP/NF limit (please see **supplementary pages 2 - 3** for Letter stating that the material will comply with the USP established limits)

Based on this data, we propose that routine testing of in Carbomer 934P, NF is not necessary.

3. Please provide the organic volatile impurities, testing results for Carbomer 934P NF, Lot 4300-R, since this test was not required by your old specifications for Carbomer 934P NF, coded as and also was not performed in the reassays dated January 24, 1997.

Response

Carbomer 934P, NF) supplied by is not manufactured with, nor does it contain any residuals of, (please refer to the Letter from presented as **supplementary page 5**). For details on solvents used in the manufacturing process, please also refer to the DMF the Letter of Access to which is provided in **supplementary page 4.**

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4. **On the manufacturer's certificate of analysis for propylene glycol USP, a chemicals lot number, is indicated on the bottom of the testing results and a hand writing is also found on the same paper which is used as the manufacturer's lot number. Please clarify.**

Response

In order to clarify this point, we have contacted and the testing laboratory that performed the testing of propylene glycol for them. As explained in the footnote in the C of A for propylene glycol (page 928 of the ANDA), only the reduced (partial) testing was performed on this particular lot of material, correctly identified as Full testing had been performed previously on a representative lot , indicated at the bottom of the page, and the results were transcribed onto the C of A for (submitted here as **supplementary page 6**).

5. **Please add material reconciliation limits at the end of bulk manufacturing and packaging.**

Response

Please note that the material reconciliation limits at the end of bulk manufacturing and packaging have been indicated in the master manufacturing and packaging documents, included in the original ANDA. Please see the following pages of the ANDA: 954, 962 (for manufacturing) and 974, 982 and 990 (for packaging), also included in this response as **supplementary pages 7 - 11**.

6. **A blank packaging material specifications for printed tubes was provided, but all tubes tested were based on the specifications for non-printed tubes. Please clarify which packaging material specifications will be used for the future production batch.**

Response

It is Taro's normal practice to package exhibit batches of the product into non-printed tubes. Therefore the certificates of analysis for the tubes used to package the exhibit batch of Clobetasol Propionate Gel, 0.05% has been provided in the ANDA (pages 1072 - 1088).

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Upon approval, the product will be packaged into identical but printed tubes, which will be tested according to the specifications for printed tubes, presented in the ANDA (pages 1068-1071) and here for ease of reference as **supplementary pages 12 - 15**.

7. **A expiry date is defined for the test in the packaging material specifications. However, when the 30 g and 60 g tubes were used in the executed batch, S118-5994, their tests were already expired. Please comment.**

Response

Please note that the expiry date indicated in the specifications for metal tubes under the test, does not pertain to the test itself, but to the test solution used for testing (please see ANDA page 1086 - **supplementary page 16**). The solutions used to test and release the tubes in which the exhibit batch was packaged, were all within the expiry at the time of testing. Prior to packaging the product, the lots of metal tubes used to package the exhibit batch were fully tested and released, meeting all specification limits.

8. **Please submit a container/closure testing commitment that should include performing the tests for every lot of packaging components received and the packaging component remaining in inventory for certain time after its original released.**

Response

Taro commits to test every lot of packaging components to be used for packaging of Clobetasol Propionate Gel, 0.05%, upon receipt at Taro, and retest it every three years after the original release.

9. **Please add a viscosity test and establish limits for pH and impurities, including individual and total, in the finished product release specifications.**

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Response

Finished packaged product release specifications have been revised to indicate the following limits:

pH:	4.5 - 6.0	(based on the in-process limits for pH and on those proposed in the USP 23 for other dosage forms of Clobetasol Propionate)	
Impurities:	Individual	NMT	%
	Total	NMT	% (based on the data collected to date)

Viscosity test has also been included in the release specifications for packaged product. Limits for viscosity will be established based on the data obtained on the first three validation batches. A CBE supplement proposing these limits will be submitted to the Agency prior to marketing the product.

Revised finished packaged product specifications are provided in **supplementary page 17**.

In addition, Taro has revised the in-process and bulk specifications to include the test for blend uniformity, as per current FDA policy (please see **supplementary page 18**).

10. Since the supply of Clobetasol Propionate related compound A is available, please revise the assay method to include a system suitability test by using Clobetasol Propionate related compound A as described in the second supplement of USP 23 and re-evaluate this method as the method validation report stated.

Response

The test method SOP ;, submitted in our original ANDA, has now been replaced by the superior procedure SOP A-188-2, which will be used to test both active raw material and the dosage form Clobetasol Propionate Topical Solution, and as such has been fully validated. The system suitability test including related compound A, as described in the USP 23, Supplement 2, has also been included in the SOP A-188-2.

Please see **supplementary pages 19 - 23** for the SOP A-188-2, and **supplementary pages 24 - 95** for the Validation Report RD-MV051.

Please note that this active substance test method, SOP A-188-2, has also been submitted with the ANDA No. 75-224 for Clobetasol Propionate Topical Solution USP, 0.05%.

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11. Please add a formula in the assay method for calculating the related compounds detected in Clobetasol Propionate raw material.

Response

The SOP A-188-2, described as per point 10, and submitted in **supplementary pages 19 - 23**, indicates the formula for calculation of related compounds levels, found in the raw material Clobetasol Propionate.

12. Based on the current USP, the method validation for the assay method should include studies of ruggedness and limit of detection. Please provide the results of these studies.

Response

Method Validation Report RD-MV051, provided in **supplementary pages 24 - 95**, includes studies of ruggedness and limit of detection for the new method, SOP A-188-2, showing acceptable results for both parameters. Please see pages 7 - 12 and 18 - 22 of the Validation Report.

13. Although the resolutions between Clobetasol Propionate and related compound A are found in the range of as shown in the chromatogram on page 1334 and 1335 of the application, the Clobetasol Propionate and related compound A peaks are not adequately resolved from each other, which you are already aware and stated in the method validation report To avoid a potential interference during assay, please revise the requirement of resolution between Clobetasol Propionate and related compound A.

Response

While the Method Validation Report pertains to the test method SOP for the assay of active in the raw material, the chromatograms indicated in the above comment are taken from a different validation report referring to the different method (SOP for assay of clobetasol propionate in Clobetasol Propionate Gel.) Test method SOP assures satisfactory resolution between peaks of Clobetasol 17-propionate and RCA, thus minimizing the risk of interference between these two components. Please see **supplementary page 96** (ANDA page 1294) for the representative chromatogram.

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14. All the compounds remarked with "*" in the peak identification table of assay method on page 1265 are not only potential precursors but also potential degradant based on Clobetasol Propionate degradation pathways on page 1184, therefore, they should be quantitated. Please comment.

Response

Out of the four compounds marked with "*" on page 1265 of the ANDA (**supplementary page 97**) , only three were shown to be possible degradation products: The fourth marked compound, is not shown on page 1184 of the ANDA (**supplementary page 98**) since it is not possible to generate this impurity through degradation (it is purely a synthetic impurity).
In order to establish whether the above listed three compounds are degradants actually forming in our product upon storage at room temperature and/or under accelerated conditions we have reviewed and evaluated our stability data generated until now. Results obtained for all peaks detected are shown in Table 1: Impurity Profile of Clobetasol Propionate Gel (**supplementary page 99**).

was not detected at the release of the finished packaged product neither was it present in the samples of the same batch, stored for 12 months under RT conditions and in the 3 months accelerated samples (40°C/75% RH).

A peak corresponding to the retention time of was detected at % level at the release of the finished packaged product This peak has not been detected in the 3 months accelerated samples, however it has been detected in the room temperature stability samples, as shown in Table 1.

was present at a level of about % at release. Its level was found to be the same at the 12 months RT timepoint and after being exposed to accelerated stability conditions for 3 months, indicating that this compound is not an actual, but only a hypothetical degradation product.

Based on the above, we believe there is no need to consider and as potential degradants and monitor for them in our product. However, we revised our method to accommodate the quantitation of since its level increased under normal storage conditions. A copy of the revised method, is attached in **supplementary pages 100 - 103**.

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15. Please establish limits for pH, viscosity (upper and lower limits), and impurities, including individual and total, in the stability specifications.

Response

Stability specifications have been revised to indicate the following limits:

pH:

Impurities:	Individual	NMT	%
	Total	NMT	%

Viscosity test has also been included in the stability specifications. Upper and lower limit for viscosity will be established based on the stability data (minimum 6 months), collected on the first three production batches. At that time, a CBE supplement proposing these limits will be submitted to the Agency.

Revised stability specifications are provided in **supplementary pages 104- 105.**

16. Please provide the currently available long-term stability data which should include the viscosity tests.

Response

Submitted in **supplementary pages 106 - 111**, are updated stability summaries (12 months room temperature data) obtained on the exhibit batch. Please note that the viscosity test has been included for the 6, 9 and 12-month test stations.

A. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Upon the resolution of the deficiencies of method validations indicated above, the assay methods for finished product will need to be validated by a FDA laboratory.

Response

Acknowledged.

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Please note that the test procedure SOP (which will be used to test both active raw material and the dosage form Clobetasol Propionate Topical Solution), submitted in **supplementary pages 19 - 23**, as per points 10, 11, 12 and 13 of this letter, has been already presented to the Agency with the Major Amendment for Clobetasol Propionate Topical Solution USP, 0.05%, ANDA 75-224.

2. **A satisfactory compliance evaluation of the facilities listed for drug substance and drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.**

Response

Acknowledged

Labeling Deficiencies

1. **CONTAINER (15 g, 30 g, 60 g)**

a. **Revise the content statement to read, Each gram contains: Clobetasol propionate 0.5 mg in ....**

b. **Revise the prescribing information statement to read, USUAL DOSAGE: Apply a thin layer of Clobetasol propionate gel to the affected skin areas twice daily and rub in gently and completely. See .....information.**

2. **CARTON (15 g, 30 g, 60 g)**

See CONTAINER comments.

3. **INSERT**

a. **TITLE**
Revise the second line to read, FOR TOPICAL USE ONLY.

b. **DESCRIPTION**

i. **Revise the second paragraph to use the second chemical name listed in the USP.**

ii. **Revise the first sentence of the third paragraph to read, ...molecular formula....**

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iii. **Revise the molecular weight to read, 466.98, to be in accord with the USP.**

iv. **Revise the fourth paragraph to read, Each gram, for topical administration contains clobetasol propionate 0.5 mg in .....**

Please revise your labels and labeling, as instructed above, and submit in final print. Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with tour last submission with all differences annotated and explained.

Response

The labels and labeling have been revised as instructed above. The following has been provided:

Twelve (12) final printed labels:

- 15 g tube labels (**supplementary pages 112 - 123**)
- 15 g carton labels (**supplementary pages 124 - 135**)
- 30 g tube labels (**supplementary pages 136 - 147**)
- 30 g carton labels (**supplementary pages 148 - 159**)
- 60 g tube labels (**supplementary pages 160 - 171**)
- 60 g carton labels (**supplementary pages 172 - 183**)
- Package insert (plastic pouch with the **supplementary page 184**)

Side-by-side comparison of the proposed labeling with the last submission with all differences annotated and explained is provided in **supplementary pages 185 - 199.**

This completes our response to the Agency's deficiency letter dated June 2, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A. Inc.
Attn.: Lorraine Sachs, RAC
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001

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This Major Amendment is being submitted in two copies. In addition a third (Field copy) is enclosed.

Sincerely yours,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/ V.Lucic
cc. Acting Director, FDA, Office of International Programs

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March 31, 1998

TARO PHARMACEUTICALS INC.
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Office of Generic Drugs
Food and Drug Administration
Document Control Room
MPN II
7500 Standish Place, room 150
Rockville, Maryland
USA 20857

ORIG AMENDMENT

att: Ms. Nancy Chamberlain,

Reference: ANDA 75-279
Clobetasol Propionate Gel 0.05%
Telephone Amendment

Dear Ms. Chamberlain,

Reference is made to our ANDA No. 75-279 for Clobetasol Propionate Gel 0.05%. Reference is also made to the telephone conversation of March 31, 1998 between yourself and Mrs. Lorraine Sachs of Taro Pharmaceuticals regarding assay and content uniformity results for the batches of the product used in the biostudy.

In response to your request, attached are Certificates of Analysis for the batches of Clobetasol Propionate Gel 0.05% used in the in-vivo bioequivalence study no. 9715098, as follows:

	Test Product	Reference Product
Name	Clobetasol Propionate	Temovate®
Manufacturer	Taro Pharmaceuticals Inc.	Glaxo Wellcome, USA
Lot No.	S118-5994	6J231
Assay	%	% LC

As you will note, the results for content uniformity have not been included in the Certificates of Analysis, since we do not normally perform this test on the finished packaged product intended for topical use.

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This completes our Response to the Agency's telephone request of March 31, 1998. If there are any questions with regards to this amendment, please do not hesitate to contact the undersigned or our U.S. agent

Taro Pharmaceuticals U.S.A., Inc.,
attention: Lorraine Sachs
Associate Director, Regulatory Affairs
5 Skyline Drive
Hawthorne, New York 10532

(914) 345-9001

Sincerely yours,

TARO PHARMACEUTICALS INC.

Derek Ganes, Ph. D.
Director, Regulatory Affairs

/Vesna Lucic

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February 3, 1998

TARO

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AP

Reference: **ANDA 75-279**
Clobetasol Propionate Gel, 0.05%
General Correspondence

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Clobetasol Propionate Gel, 0.05%.

Reference is also made to the letter from the Agency dated January 21, 1998 in which it was requested:

> *In the interim, please submit a diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses. For each study, two separate files should be configured as follows:*
>
> *(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$; ...*
> *(b) subj seq per trt C_1 C_2 C_3 ..... C_n*
>
> *where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).*

Enclosed please find a diskette as requested.

This completes our response to the Agency's letter of January 21, 1998.

If there are any questions with regards to this response, please do not hesitate to contact me.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

CK 1-12-98

TARO

TARO PHARMACEUTICALS INC.
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December 19, 1997

Mr. Douglas Sporn
Office of Generic Drugs
Document Control Room
CDER, FDA, MPN II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: **Original Abbreviated New Drug Application (ANDA) for Clobetasol Propionate Gel, 0.05 %**

Dear Mr. Sporn:

Taro Pharmaceuticals Inc. submits today an original Abbreviated New Drug Application (ANDA) seeking approval to market Clobetasol Propionate Gel, 0.05% that is bioequivalent to the listed drug, TEMOVATE®, manufactured by Glaxo Wellcome pursuant to NDA N20337.

This ANDA consists of 3 volumes. Taro Pharmaceuticals Inc. is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA and two (2) technical review copies (in red folders) which contain all the information in the archival copy ~~with~~ the exception of the Bioequivalence Section (VI). A separate copy of the Bioequivalence Section is provided in orange folders.

Taro Pharmaceuticals Inc. hereby certifies that, the field copy of this ANDA submission contained in burgundy folders is a true copy of the technical sections of the ANDA. The field copy also contains a copy of the signed 356h form and a certification that the contents are a true copy of the technical sections of the ANDA.

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If there are any questions regarding this application, or if additional information is required, please contact our US agent:

Taro Pharmaceuticals USA, Inc.,
Attn: Lorraine Sachs, RAC
5 Skyline Drive
Hawthorne, NY 10532
Tel: (914) 345-9001

Sincerely,
TARO PHARMACEUTICALS INC.

Derek Ganes, Ph.D.
Vice President, Regulatory Affairs

/J. Hobbs, B.Sc.

Enclosures:

Archival Copy (1 set):
All Sections (I - XX), 3 volumes (Blue)
Review Copies (2 sets):
CMC (Sections I-V and VII-XX), 1 volume (Red)
Bioequivalence (Sections I-VII): 2 volumes (Orange)
Field Copy (1 set)
CMC (Sections I-V and VII-XX), 1 volume (Burgundy)

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